S 24. *The Preparation of Potential Analgesic Compounds. Part III.*

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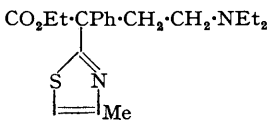
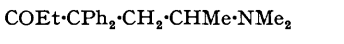
Potential analgesic compounds, typified by (III) and structurally similar to " Amidone " (II), were obtained by direct carbethoxylation or propionylation of 2-benzylthiophen, followed by introduction of a basic side chain. Certain of these products had analgesic activity. Other compounds, such as 2-*phenyl*-2-*diethylaminoethyl*cyclo*hexanone* (VI), also structurally related to " Amidone ", were prepared but were inactive.

Substances typified by (I), and thus related in structure to " Amidone " (II), were shown in Part II (preceding paper) to be inactive as analgesics. This result seemed possibly due to the basic lyophilic thiazole ring, and it appeared desirable to bring the relationship to known analgesic compounds perhaps closer in a physicochemical sense. The object was therefore to replace the thiazole ring by a thiophen system to give compounds of type (III), where R = COEt or CO_2Et. This replacement of the phenyl group of " Amidone " by a thiophen nucleus had particular interest because a similar operation in the diphenylacetic acid series (Blicke and Tsao, *J. Amer. Chem. Soc.*, 1944, **66**, 1645) led to enhanced activity.



(I.)



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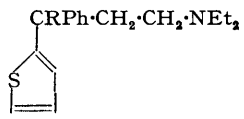
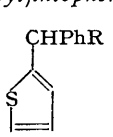


(III.)

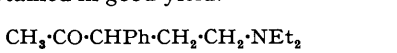
The first synthetic approach was made by analogy with the preparation of ethyl diphenylacetonitrile (Schultz *et al.*, *J. Amer. Chem. Soc.*, 1947, **69**, 2458). The reaction between bromobenzyl cyanide and thiophen in the presence of aluminium chloride proved unsatisfactory and the route was abandoned in favour of the direct preparation of 2-α-carboxybenzylthiophen. The method of Blicke and Tsao (*loc. cit.*) was not attractive because of its several steps, so a direct carboxylation of 2-benzylthiophen was attempted by analogy with the successful preparation of diphenylacetic acid by Yost and Hauser (*J. Amer. Chem. Soc.*, 1947, **69**, 2326). 2-Benzylthiophen was prepared by condensation of benzyl alcohol with thiophen in the presence of zinc chloride (Steinkopf and Hanske, *Annalen*, 1939, **541**, 238). It was converted into its monopotassium derivative with potassium amide, and this on treatment with powdered solid carbon dioxide readily gave 2-α-carboxybenzylthiophen. Esterification in the usual way gave 2-α-*carbethoxybenzylthiophen* (IV; R = CO_2Et), but it was subsequently found that treatment of the potassium derivative of 2-benzylthiophen with ethyl carbonate led in a single step to the same ester in reasonable yield.

The required basic side chain was then attached to the phenylated carbon atom. Thus, with *N*-(2-chloroethyl)diethylamine and sodamide there resulted 2-(3′-*diethylamino*-1′-*carbethoxy*-1′-*phenylpropyl*)*thiophen* (III; R = CO_2Et). Similarly from *N*-(2-chloroethyl)morpholine was obtained 2-(3′-*morpholino*-1′-*carbethoxy*-1′-*phenylpropyl*)*thiophen*, characterised as its *picrate* and *oxalate*. A branched basic chain was also introduced by means of *N*-(2-chloropropyl)morpholine to give 2-(3′-*morpholino*-1′-*carbethoxy*-1′-*phenyl*-2′-*methylpropyl*)*thiophen*.

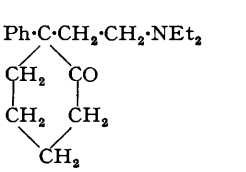
To increase the similarity to amidone still further, the potassium derivative of 2-benzylthiophen was treated with ethyl propionate to give in low yield 2-α-*propionylbenzylthiophen* (IV; R = COEt). The ketone was aminoalkylated in the same manner as the corresponding ester, to yield with *N*-(2-chloroethyl)diethylamine, 2-(3′-*diethylamino*-1′-*propionyl*-1′-*phenylpropyl*)*thiophen* (III; R = COEt), characterised as the *oxalate*. With *N*-(2-chloroethyl)- and *N*-(2-chloropropyl)-morpholine respectively 2-(3′-*morpholino*-1′-*propionyl*-1′-*phenylpropyl*)-*thiophen* (characterised as its *hydrogen oxalate*) and 2-(3′-*morpholino*-1′-*propionyl*-1′-*phenyl*-2′-*methylpropyl*)*thiophen* were obtained in good yield.



(IV.)



(V.)



(VI.)

During the present work the opportunity was taken to examine another structural type based essentially on the ketones typified by 1-diethylamino-3-phenylpentan-4-one (V) (cf. Part I, this vol., p. S 107); represented by (VI), it also approached amidone in the pattern of its structure.

*cyclo*Hexanone was chlorinated, and the resulting 2-chloro*cyclo*hexanone reacted with phenylmagnesium bromide (Newman and Farbman, *J. Amer. Chem. Soc.*, 1944, **66**, 1550) to give 2-phenyl*cyclo*hexanone. The latter was then aminoalkylated in presence of sodamide. From *N*-(2-chloroethyl)diethylamine was obtained 2-*phenyl*-2-*diethylaminoethyl*cyclo*hexanone* (VI), from *N*-(2-chloropropyl)morpholine 2-*phenyl*-2-(2′-*morpholino*-1′-*methylethyl*)cyclo*hexanone*, and from *N*-(2-chloroethyl)morpholine 2-*phenyl*-2-*morpholinoethyl*cyclo*hexanone* which was characterised as its *acid oxalate*.

Most of the above compounds were tested for analgesic activity. Those represented by (VI) proved devoid of interest in this connection. Some of the thiophen derivatives, however, by contrast with the comparable thiazole compounds, displayed some activity. For instance, judged by a standardised test, (III; R = COEt) had one-third of the activity of pethidine, and 2-(3′-morpholino-1′-carbethoxy-1′-phenylpropyl)thiophen was four times as effective as pethidine.

Experimental.

A 1-litre three-necked flask was fitted with an efficient sealed stirrer carrying some rusty iron wire on the blades, a solid carbon dioxide–alcohol reflux condenser, and a dropping-funnel. To liquid ammonia (200 c.c.) in this apparatus was added potassium (5·4 g.) in small pieces during 10 minutes with stirring. When amide formation was complete, as shown by the disappearance of the blue colour, the reflux condenser was replaced by a water condenser, and 2-benzylthiophen (22 g.) in dry ether (250 c.c.) was added dropwise. The flask was gently warmed to remove ammonia and then the ethereal suspension was refluxed for 2 hrs.

To the product, after cooling, was added powdered solid carbon dioxide (*ca.* 200 g.) during 20 mins. After 1 hr., cold water (200 c.c.) was added, the whole shaken, and the aqueous layer separated and acidified. The semi-solid precipitate was collected, dissolved in 1N-sodium hydroxide (100 c.c.) and the solution just neutralised with stirring with 2N-hydrochloric acid. The suspension was filtered and 2-α-carboxybenzylthiophen (7·7 g.), m. p. 105—110°, precipitated by excess of acid. Recrystallisation from aqueous ethanol gave white needles, m. p. 113° (lit., m. p. 114°).

2-α-Carboxybenzylthiophen (6·6 g.), dry ethanol (28 c.c.), and sulphuric acid (1·3 c.c.) were refluxed on the steam-bath for 6 hrs. The cooled solution was added to ice-water (60 c.c.), and the oil extracted with ether. The extract was washed with dilute sodium hydrogen carbonate solution and water. Distillation gave 2-α-*carbethoxybenzylthiophen* (4·5 g.) as a colourless liquid, b. p. 123°/0·1 mm., $n_D^{15°}$ 1·5652 (Found: C, 68·1; H, 5·8; S, 12·95. $C_{14}H_{14}O_2S$ requires C, 68·3; H, 5·7; S, 13·0%).

Direct carbethoxylation of 2-benzylthiophen was also satisfactory. To an ethereal suspension of the potassium derivative of 2-benzylthiophen (see above) was added dropwise ethyl carbonate (7·5 g.) in dry ether (60 c.c.). After refluxing with stirring for 2 hrs., the cooled solution was added to ice-water (200 c.c.) and acetic acid (10 c.c.). Fractionation of the oil from the ethereal layer gave unchanged 2-benzylthiophen (b. p. 90—93°/0·1 mm., 8·7 g.) and 2-α-carbethoxybenzylthiophen, b. p. 125—135°/0·1 mm. Refractionation gave a colourless liquid (5·7 g.); b. p. 122—125°/0·1 mm., $n_D^{19°}$ 1·5640 (Found: C, 68·7; H, 5·9%).

To 2-α-carbethoxybenzylthiophen (9·2 g.) in dry toluene (40 c.c.) were added *N*-(2-chloroethyl)-diethylamine (5·6 g.) and powdered sodamide (1·6 g.). The solution became very dark on warming, with evolution of ammonia, and was refluxed gently with stirring for 2½ hrs., during which the colour lightened again. The mixture was cooled, water added, and the toluene layer dried and fractionated. 2-(3′-*Diethylamino*-1′-*carbethoxy*-1′-*phenylpropyl*)*thiophen* (6·5 g.) was obtained as a colourless oil, b. p. 155—157°/0·1 mm., $n_D^{17°}$ 1·5421 (Found: C, 69·2; H, 8·0; N, 4·05; S, 9·2. $C_{20}H_{27}O_2NS$ requires C, 69·2; H, 7·9; N, 4·05; S, 9·3%).

In the same way from 2-α-carbethoxybenzylthiophen (8 g.), *N*-(2-chloroethyl)morpholine (5·4 g.), and sodamide (1·4 g.), was obtained 2-(3′-*morpholino*-1′-*carbethoxy*-1′-*phenylpropyl*)*thiophen* (4·3 g.), as a viscous oil, b. p. 185—158°/0·4 mm., $n_D^{20°}$ 1·5610 (Found: C, 66·4; H, 7·3; N, 4·1; S, 8·7. $C_{20}H_{25}O_3NS$ requires C, 66·8; H, 7·0; N, 3·9; S, 8·9%). The *oxalate* crystallised from dioxan in laths, m. p. 190° (Found: N, 3·65. $C_{20}H_{25}O_3NS,\frac{1}{2}C_2H_2O_4$ requires N, 3·5%). The *picrate* recrystallised from ethanol to give irregular plates, m. p. 144—145° (Found: N, 9·6. $C_{26}H_{28}O_{10}N_4S$ requires N, 9·5%).

Likewise, from 2-α-carbethoxybenzylthiophen (3·6 g.) and *N*-(2-chloropropyl)morpholine (2·6 g.) with sodamide (0·7 g.) was isolated as a viscous yellow oil, b. p. 193—196°/0·3 mm., 2-(3′-*morpholino*-1′-*carbethoxy*-1′-*phenyl*-2′-*methylpropyl*)*thiophen* (1·7 g.), $n_D^{20°}$ 1·5605 (Found: C, 67·7; H, 7·4; N, 3·9. $C_{21}H_{27}O_3NS$ requires C, 67·5; H, 7·3; N, 3·75%).

An ethereal suspension of the potassium derivative of 2-benzylthiophen was prepared on twice the scale used above. To it was added, dropwise, ethyl propionate (13 g.) in dry ether (50 c.c.), and the mixture was stirred while refluxing for 2½ hours. It was cooled, and water (300 c.c.) and crushed ice (150 g.) were rapidly added. The solution was acidified with hydrochloric acid, and the ethereal layer freed from acid. The residue after removal of ether was fractionated, and the fraction, b. p. 125—135°/0·4 mm., redistilled to give 3·8 g. of a 2-α-*propionylbenzylthiophen* as a slightly yellow oil, b. p. 125—127°/0·5 mm., $n_D^{18°}$ 1·5800 (Found: C, 73·5; H, 6·25; S, 13·6. $C_{14}H_{14}OS$ requires C, 73·0; H, 6·15; S, 13·9%).

To 2-α-propionylbenzylthiophen (2·5 g.) and *N*-(2-chloroethyl)diethylamine (1·6 g.) in dry toluene (15 c.c.) was added with stirring powdered sodamide (0·5 g.). After 15 mins. the solution was refluxed gently with stirring for 2 hrs. To the cooled solution was added water, and the toluene layer was fractionated to give 1·5 g. of the colourless oily 2-(3′-*diethylamino*-1′-*propionyl*-1′-*phenylpropyl*)-

thiophen, b. p. 158—160°/0·4 mm., $n_D^{21°}$ 1·5655 (Found : C, 72·95; H, 8·25; N, 4·2; S, 9·4. $C_{20}H_{27}ONS$ requires C, 72·9; H, 8·25; N, 4·25; S, 9·7%). The *oxalate* crystallised from dioxan to give laths, m. p. 118—120° (decomp.) (Found : N, 3·6. $C_{20}H_{27}ONS,\frac{1}{2}C_2H_2O_4$ requires N, 3·7%).

Likewise, from 2-α-propionylbenzylthiophen (3·7 g.), *N*-(2-chloroethyl)morpholine (2·7 g.), and sodamide (0·75 g.) were obtained 2·8 g. of the colourless oily 2-(3′-*morpholino*-1′-*propionyl*-1′-*phenylpropyl*)*thiophen*, b. p. 185—188°/0·2 mm., $n_D^{20°}$ 1·5845 (Found : C, 70·6; H, 7·4; N, 4·0. $C_{20}H_{25}O_2NS$ requires C, 70·0; H, 7·35; N, 4·1%). The *hydrogen oxalate* recrystallised from dioxan in plates, m. p. 191° (decomp.) (Found : N, 3·15. $C_{22}H_{27}O_6NS$ requires N, 3·2%).

In a similar way from 2-α-propionylbenzylthiophen (3·8 g.), *N*-(2-chloropropyl)morpholine (3·0 g.), and sodamide (0·8 g.) were produced 3·1 g. of colourless viscous 2-(3′-*morpholino*-1′-*propionyl*-1′-*phenyl*-2′-*methylpropyl*)*thiophen*, b. p. 188—190°/0·2 mm., $n_D^{20°}$ 1·5796 (Found : C, 70·8; H, 7·3; N, 3·95. $C_{21}H_{27}O_2NS$ requires C, 70·5; H, 7·6; H, 3·95%).

2-Phenyl*cyclo*hexanone (17·4 g.; Newman and Farbman, *loc. cit.*), *N*-(2-chloroethyl)diethylamine (16·5 g.), and powered sodamide (4·2 g.) were refluxed gently with stirring in toluene (50 c.c.) for 3 hrs. To the cooled solution water was added, and the toluene layer extracted with 1N-hydrochloric acid (100 c.c.). On being kept for a few hours the extract deposited 3 g. of unchanged 2-phenyl*cyclo*hexanone. After filtration, the bases were liberated with sodium hydroxide and extracted with ether. Fractionation gave 2·1 g. of the viscous, yellow, oily 2-*phenyl*-2-*diethylaminoethyl*cyclo*hexanone*, b. p. 135—138°/0·05 mm., $n_D^{17°}$ 1·5205 (Found : N, 4·95. $C_{18}H_{27}ON$ requires N, 5·1%). Similarly, from 2-phenyl*cyclo*hexanone (17·4 g.), *N*-(2-chloropropyl)morpholine (18 g.), and sodamide (4·2 g.) were obtained 1·2 g. of viscous 2-*phenyl*-2-(2′-*morpholino*-1′-*methylethyl*)cyclo*hexanone*, b. p. 160—162°/0·1 mm., $n_D^{17°}$ 1·5330 (Found : N, 4·8. $C_{19}H_{27}O_2N$ requires N, 4·65%). In like manner, from 2-phenyl*cyclo*hexanone (17·4 g.), *N*-(2-chloroethyl)morpholine (17·4 g.), and sodamide (4·2 g.) were isolated 1·7 g. of 2-*phenyl*-2-2′-*morpholinoethyl*cyclo*hexanone* as an oil, b. p. 155—158°/0·05 mm., $n_D^{21°}$ 1·5338 (Found : N, 5·0. $C_{18}H_{25}O_2N$ requires N, 4·9%). The *hydrogen oxalate* formed slightly hygroscopic plates, m. p. 160°, from dioxan (Found : N, 3·8. $C_{20}H_{27}O_6N$ requires N, 3·7%).

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